REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. No claim is allowed. Claims 1-9, 11, 14, and 15 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The specification has been objected to as failing to provide proper antecedant basis for the claimed subject matter.

The title of the invention is now amended to provide consistency with the titles of the invention in parent application no. 09/050,249, in grandparent application no. 08/502,535, now issued as U.S. Patent no. 5,912,324, and in 08/908,005 (divisional of 08/502,535) now issued as U.S. Patent no. 5,914,253. Applicants submit that the terms "IGIF" or "IL-18" are new names given in the art to the "interferon-gamma production inducing protein" according to the present invention. Applicants at first called the claimed protein "interferon-gamma production inducing protein" based on its function because it was a novel protein that was unnamed at the time the present invention was made. Afterwards, during prosecution of the parent and grandparent applications, the "interferon-gamma inducing protein" became known at first by persons in the art as "IGIF" for interferon-gamma production inducing factor and then as "IL-18". Thus, the interferon-gamma inducing protein is also

known as "IGIF" and "IL-18", which are simply commonly used names for the same protein. Copies of U.S. Patent nos. 5,912,324 and 5,914,253 are attached hereto.

Reconsideration and withdrawal of this objection are therefore respectfully requested.

The specification is also objected as using terminology, specifically "antioncotic agent" which is not generally accepted in the art and whose meaning cannot be determined.

Applicants attach hereto relevant pages of Dorland's Illustrated Medical Dictionary, 25th edition, W.B. Saunders, Philadelphia, PA, 1974, where "antioncotic" is defined as accepted in the art.

The specification is further objected to because of the inconsistent use of SEQ ID Nos. The newly amended paragraph replacing the third paragraph at page 9 of the specification uses SEQ ID NO:3 instead of SEQ ID NO:2 which was used in the previous version as indicated in the preliminary amendment filed August 12, 1999.

Applicants' clarify that the use of SEQ ID NO:3 in the newly amended paragraph was an inadvertent error. SEQ ID NO:2 was intended as would be understood from the preliminary amendment filed August 12, 1999, which provided consistency between the sequence identifiers in the specification and in the

Sequence Listing and with parent and grandparent applications. Appropriate correction is now made to the specification.

Reconsideration and withdrawal of these objections are therefore respectfully requested.

Claims 1-3, 7, 11, and 12 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The examiner states that applicants have not pointed out, nor can the examiner locate, the basis in the specification for the newly introduced recitation of "IGIF" and/or "IL-18" in these claims. This rejection is respectfully traversed.

As discussed above with respect to the objection to the specification, the terms "IGIF" and "IL-18" are simply different names used for the same protein, the IFN-γ inducing protein according to the present invention. Applicants submit that this is not new matter, as the examiner in charge of handling the related applications, which issued as U.S. Patent nos. 5,912,324 and 5,914,253, well recognized.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 1-9 and 11-15 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

Regarding claims 1-3 and 11, the examiner states that it is unclear whether part of SEQ ID NO:2 has to include the region where Xaa is, or any part of SEQ ID NO:2 is acceptable.

Met or Thr for Xaa only refers to SEQ ID NO:2. The presently claimed protein contains a part of SEQ ID NO:2 but does not necessarily contain the part of SEQ ID NO:2 where Xaa is Met or Thr. This is made clear by the amendment to claims 1-3 and 11.

This rejection as it relates to the recitation of IGIF and IL-18 is believed to be overcome by the amendments to claims 93 and 118 and the discussion above regarding the terms "IGIF" and "IL-18" as simply different art recognized names used for the IFN-γ inducing protein according to the present invention.

With regard to the language "not substantially altering", which means "substantially the same", in claims 3 and 11, applicants submit that this language is not indefinite. The Court of Appeals held in *Arnold Pipe Rentals Company, Inc. v Engineering Enterprises*, 146 USPQ 416, that absolute precision in wording of claims, while desirable, would be an unreasonable burden to impose on inventor and that descriptive words such as "substantial", "high", "about", and "slight excess" have often

withstood attack under 35 U.S.C. 112; thus, "at least substantially flat" is not fatally indefinite. Attached hereto are copies of U.S. Patents 6,156,315 (issued within the past year) and 5,429,936, which accepted the use of the claim language "substantially the same."

The remaining indefiniteness issue with respect to claim 12 is obviated by the cancellation without prejudice of claim 12.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claim 3-6 remain rejected under 35 U.S.C. 112, first paragraph, because the examiner states that the specification, while being enabling for claims limited in scope to a specific variant of said protein, which has an amino acid sequence of SEQ ID NO:2 where residue 70 is methionine or threonine, does not reasonably provide enablement for claims to variants having physiochemical and functional properties listed in parts (1) to (4) of claim 3, and having the amino acid sequence of SEQ ID NO:2 with at least one amino acid residue in SEQ ID NO:2 replaced with a different amino acid, or at least one amino acid residue deleted or added to the N-terminus of SEQ ID NO:2 while not substantially altering physicochemical properties of the protein.

Claims 1, 2, and 11-15 have also been rejected under 35 U.S.C. 112, first paragraph, because the examiner states that the specification, while being enabling for claims limited in scope to a protein with SEQ ID NO:2, wherein residue 70 is methionine or threonine, does not reasonably provide enablement for variants with properties listed in these claims.

Claims 1-6, and 11-15 have been further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filled, had possession of the claimed invention. These rejections under 35 U.S.C. §112, first paragraph, are respectfully traversed.

The rejections as they may relate to claims 12 and 13 are obviated by the cancellation without prejudice of rejected claims 12 and 13.

At the time claimed invention was made, it was possible for the skilled artisan to obtain variants based on the amino acid sequence of SEQ ID NO:2 (wherein Xaa is Met or Thr) by replacing one or more amino acids with different ones, or by deleting one or more amino acids from, or by adding one or more amino acids to, SEQ ID NO:2. See U.S. Patent No. 5,304,496, a copy of which is attached. It is therefore believed that it would have been possible for the skilled artisan at the time the

claimed invention was made to screen for variants based on their physiochemical properties to find the proteins having the physicochemical properties as recited in (1) to (3) of claim 3 and to obtain the variants of claim 3 without undue experimentation once the amino acid sequence of SEQ ID NO:2 is known.

The examiner also states that to the extent that the claims encompass antibodies that bind to epitopes not found in the particularly disclosed sequences, there is no written description of those epitopes. However, the examiner's requirement is not a realistic one. It is impossible (even for the skilled person) to check if a monoclonal antibody to a certain polypeptide binds to other polypeptides and disclose the results in the specification. In fact, the applicants are aware of no patent specification issued in the United States and other countries that checks if a monoclonal antibody to a certain polypeptide binds to other polypeptides and disclose the results in it. It is in fact impossible to check and confirm that a monoclonal antibody to a certain polypeptide, while specifically binding to the polypeptide, never binds to other polypeptides.

When a skilled person intends to obtain a monoclonal antibody against a polypeptide X, the skilled person can easily obtain the monoclonal antibody that specifically binds to

polypeptide X without undue experimentation if the polypeptide X or its sequence is provided.

Claim 11 has been rejected on the same grounds as in claims 3-6. Applicants believe that claim 11 is amended to define precisely the claimed variants. Such variants as defined in claim 11 are obtainable without undue experimentation based on the amino acid sequence of SEQ ID NO:2 and the state of the art, such as shown, in "MOLECULAR BIOLOGY OF THE GENE", The Benjamin/Cummings Publishing Company, Inc., pp. 226-229 (1987), a copy of which is attached.

Reconsideration and withdrawal of the rejections are therefore respectfully requested.

Claims 3 and 5-6 remain rejected under 35 U.S.C. §102(b) as being anticipated by Nakamura et al. Furthermore, claims 1, 2, and 11-15 have also been rejected under 35 U.S.C. §102(b) as being anticipated by Nakamura et al. These rejections are respectfully traversed.

With due respect to the examiner, Nakamura never discloses the protein as defined in claims 3 and 5-6. The protein of Nakamura is distinct from the presently claimed protein on the following grounds. An "interferon-gamma (IFN-γ) inducing protein, also known as (IGIF and IL-18) of the present invention shows a molecular weight of 19,000±5,000 daltons on SDS-PAGE. By contrast, the factor of Nakamura shows a molecular

weight of 50,000-55,000 (50-55 kDa) using the same method (see page 66, right lower column and page 67, left upper column, Fig. 2). The difference is significant. The fact that the molecular weights measured with the same method are different means that the two substances are different.

The examiner states that if the factor of Nakamura is a polymer of an "interferon-gamma (IFN-γ) inducing protein" of the present invention, also known as IGIF and IL-18, then the difference can be explained. However, it should be noted that Nakamura never confirmed the presence of IGIF having a molecular weight of 19,000±5,000 daltons by purification and separation.

Furthermore, Nakamura discloses at page 68, right column, second paragraph, that Nakamura's factor having a molecular weight of 50-55 kDa loses IFN-γ inducing activity after the treatment on SDS-PAGE. By contrast, IGIF having a molecular weight of 19,000±5,000 daltons maintains its IFN-γ inducing activity after treatment on SDS-PAGE as shown at page 23, middle paragraph, Experiment 2. It is therefore believed that IGIF of the claimed invention and Nakamura's factor are clearly different on the following points;

(a) molecular weight;

(b) there are no descriptions in Nakamura which suggests that Nakamura's factor is a polymer of the IGIF of the

claimed invention and which discloses that a monomer is actually purified and separated; and

(c) Nakamura's factor loses its IFN-γ inducing activity when treated on SDS-PAGE.

Thus, Nakamura never discloses or suggests the presently claimed protein. It is therefore believed that the claimed invention is not anticipated by the disclosure of Nakamura.

Reconsideration and withdrawal of the rejections are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

IN THE TITLE

The title has been amended as follows:

--IFN-γ PRODUCTION INDUCING PROTEIN (IGIF, IL-18) ~~MONOCLONAL ANTIBODY OF THE SAME~~--

IN THE SPECIFICATION

The paragraph beginning at page 9, line 7, has been amended as follows:

The protein according to the present invention includes proteins in general which have specific physicochemical properties and those derived from natural sources and those prepared by the recombinant DNA technology. The present protein generally has a partially or totally revealed amino acid sequence, for example, the amino acid sequence containing the N-terminal in SEQ ID NO:~~3~~2 and its homologous amino acid sequences. Variants, which have homologous amino acid sequence to the one in SEQ ID NO:~~3~~2, can be obtained by replacing one or more amino acids in SEQ ID NO:~~3~~2 with other amino acids without alternating the inherent biological properties of the present protein. Even when used the same DNA and depending on hosts into which the DNA is introduced, as well as on the components of nutrient culture media, the conditions of cultivation temperature and pH for culturing transformants containing the

DNA, it may be formed variants, which are defective in or additionally contain one or more amino acids near to the N-terminal in SEQ ID NO:~~3~~2 while retaining the inherent biological properties of the protein, by the modification with internal enzymes of the hosts after the DNA expression. The present protein includes such variants as long as they induce the IFN-γ production by immunocompetent cells.

IN THE CLAIMS

Claims 1-3, 7, 8, 11, and 14 have been amended as follows:

1(Twice-amended). An IFN-γ production inducing agent which consists essentially of an effective ingredient capable of inducing IFN-γ production by immunocompetent cells, said effective ingredient consisting of ~~a protein (IGIF, IL-18)~~ an interferon-gamma (IFN-γ) production inducing protein, also known as IGIF and IL-18, having the following physicochemical properties:

(1) Molecular weight

19,000±5,000 daltons on gel filtration and sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE);

(2) Isoelectric point (pI)

4.8 ± 1.0 on chromatofocusing;

(3) Biological activity

Inducing the interferon-γ production by immunocompetent cells; and

(4) Partial amino acid sequence

Possessing a part or the whole of the amino acid sequence of SEQ ID NO:2, wherein the Xaa in SEQ ID NO:2 is Met or Thr.

2(Twice-amended). A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and an effective ingredient capable of inducing IFN-γ production by immunocompetent cells, said effective ingredient consisting of ~~a protein (IGIF, IL-18)~~ an interferon-gamma (IFN-γ) production inducing protein, also known as IGIF and IL-18, having the following physicochemical properties:

(1) Molecular weight

19,000±5,000 daltons on gel filtration and sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE);

(2) Isoelectric point (pI)

4.8 ± 1.0 on chromatofocusing;

(3) Biological activity

Inducing the interferon-γ production by immunocompetent cells; and

(4) Partial amino acid sequence

Possessing a part or the whole of the amino acid sequence of SEQ ID NO:2, wherein the Xaa in SEQ ID NO:2 is Met or Thr.

3(Twice-amended). A purified interferon-gamma (IFN-γ) production inducing protein which is a variant of ~~a protein (IGIF, IL-18)~~ an interferon-gamma production inducing protein, also known as IGIF and IL-18, having the following physicochemical properties:

(1) Molecular weight

19,000±5,000 daltons on gel filtration and sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE);

(2) Isoelectric point (pI)

4.8 ± 1.0 on chromatofocusing;

(3) Biological activity

Inducing the interferon-γ production by immunocompetent cells; and

(4) Partial amino acid sequence

Possessing a part or the whole of the amino acid sequence of SEQ ID NO:2, wherein the Xaa in SEQ ID NO:2 is Met or Thr, wherein said variant has the amino acid sequence of SEQ ID NO:2 with at least one amino acid residue in SEQ ID NO:2 replaced with different amino acid or at least one amino acid residue deleted or added to the N-terminus of SEQ ID

NO:2 while not substantially altering the physicochemical properties of the protein.

7(Twice-amended). A purified interferon-gamma (IFN-γ) production inducing protein, also known as IGIF and IL-18, ~~protein (IGIF, IL-18)~~ which has the amino acid sequence of SEQ ID NO:2, where Xaa represents methionine or threonine.

8(Twice-amended). An interferon-gamma (IFN-γ) production inducing agent which consists essentially of, as an effective ingredient, the protein of claim 7.

11(Once-amended). A purified interferon-gamma (IFN-γ) production inducing protein, also known as IGIF and IL-18 ~~protein (IGIF, IL-18)~~, which has the following physicochemical properties:

(1) Molecular weight

19,000±5,000 daltons on gel filtration and sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE);

(2) Isoelectric point (pI)

4.8 ± 1.0 on chromatofocusing;

(3) Biological activity

Inducing the interferon-γ production by immunocompetent cells; and

(4) Partial amino acid sequence

Possessing a part or the whole of the amino acid sequence of SEQ ID NO:2, wherein the Xaa in SEQ ID NO:2 is Met or Thr,

and which reacts with a monoclonal antibody specific to ~~a~~ an interferon-gamma production inducing protein having the amino acid sequence of SEQ ID NO:2 or a variant of the protein having one or more antigenic fragments of the amino acid sequence of SEQ ID NO:2 and an ~~the~~ amino acid sequence of SEQ ID NO:2 with at least one amino acid residue in SEQ ID NO:2 replaced with a different amino acid, or at least one amino acid residue deleted or added to the N-terminus of SEQ ID NO:2, while not substantially altering the physicochemical properties of the protein.

14(Once-amended). A purified interferon-gamma (IFN-γ) production inducing protein capable of inducing interferon-gamma (IFN-γ) production by immunocompetent cells, wherein said protein is encoded by a DNA sequence which hybridizes to an oligonucleotide probe of SEQ ID NO:5 under the hybridization conditions of 5 x SSPE, 5 x Denhardt's solution, 0.5 w/v% SDS, 100 µg/ml denatured salmon sperm DNA, and 45°C and after being washed with 6 x SSC.